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EXAMINER	
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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 20060522

Application Number: 09/148,012
Filing Date: September 04, 1998
Appellant(s): KRIEGER, MONTY

Rivka Monheit
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 5/15/06.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The amendment after final rejection filed on 1/17/06 has been entered.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the grounds of rejection to be reviewed on appeal is substantially correct. The changes are as follows: claims 10 has been canceled and claim 19 has been withdrawn.

(7) Grouping of Claims

Appellant's brief includes a statement that claims 1-9, 12, 15, 16 and 19-22 do not stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) Claims Appealed

The statement of the status of the claims contained in the brief is incorrect. A correct statement of the status of the claims is as follows: Claim 19 is withdrawn from consideration as not directed to the elected invention.

(9) Prior Art of Record

No prior art is relied upon by the examiner in the rejection of the claims under appeal.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 112, first paragraph – written description

Claims 1-9, 12, 15, 16 and 20-22 are rejected under 35 U.S.C. 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was

filed, had possession of the claimed invention. Claim 1, from which all of these rejected claims ultimately depend, recites a method for altering fertility, or treating a reproductive disorder in a female mammal in need of treatment comprising administering a compound which alters lipoprotein, LDL, HDL, or cholesterol levels in the mammal.

These are genus claims. The claims encompass a universe of compounds. However, Appellant has only provided written description of a small number of specific compounds which act via SR-BI, including estrogen (Example 3 on pages 39-40 of the specification), adenoviral vector encoding SR-BI (Example 5 on pages 40-45 of the specification), and anti-SR-BI antibody (Example 8 on pages 55-66 of the specification) to alter cholesterol levels. However, Appellant has provided no written description of any compounds which alter *fertility* or treat reproductive disorders by altering lipoprotein, LDL, HDL, or cholesterol levels in the mammal. Appellant has only described that knocking out the SR-BI gene produces sterile (i.e. altered fertility) transgenic female mice (Example 6, pages 45-54 of the specification).

Furthermore, claims 1-7, 15, 16 and 19-22 recite, or read on, altering SR-BI receptors, or affecting receptor binding to lipoproteins, in *any* tissue. Appellant has not provided adequate written description of which specific tissues modulation of SR-BI would be required in order to alter fertility or to treat *any and all* reproductive disorders. Appellant has only demonstrated that completely knocking out the SR-BI gene (i.e. from all tissues) causes female mice to be infertile (Example 6). However, in the other examples in the specification, Appellant does not describe how altering SR-BI levels in these tissues alone affects fertility or reproductive disorders in a mammal, or if altering SR-BI levels *at all* in these tissues is sufficient to alter fertility or treat *any and all* reproductive disorders in a mammal. For example, in Examples 3 and 4, Applicants have only shown that estrogen-treated rats show an upregulation of SR-BI in adrenal membranes (page 39, line 30 – page 40, line 1) and ovaries (page 40, lines 20-23). Appellants have also demonstrated the effect of hepatic SR-BI overexpression on plasma cholesterol levels (Example 4, especially page 41, lines 12-14 and Table 1). Again, no nexus between SR-BI expression in these tissues and the ability to alter fertility or reproductive disorders has been described.

Additionally, Appellant has not recited the appropriate dosages of any compounds to alter fertility or treat any and any possible reproductive disorders, nor have they described to what extent the lipoprotein, LDL, HDL, or cholesterol levels need to be altered in the mammal to effectively alter fertility or to effectively treat any and all reproductive disorders. There is also no written description as to what length of time these compounds would need to be administered in order to alter fertility or to treat any and all reproductive disorders. Though fertility and reproductive disorders *may* all be affected by lipoprotein,

LDL, HDL, or cholesterol levels, they likely all have a different mechanism of action since they are all different conditions and Appellant has not adequately described these conditions (e.g. disorders), nor what level of alteration of lipoprotein, LDL, HDL, or cholesterol levels in a mammal would be required.

Appellants argue that the disclosure of estrogen, a vector encoding SR-BI and an anti-SR-BI antibody provide broad support for a genus claim. However, though these three means of altering cholesterol are encompassed by the desired genus, they, alone, do not provide adequate written description for the entire genus of compounds able to alter fertility. In addition, Appellants, respectfully, have argued numerous times that estrogen is not encompassed by the claimed invention. Regardless, it would be expected that a nucleic acid encoding the target receptor, or an antibody against the target receptor would have the desired effects. Though these compounds have been shown to alter cholesterol levels in a mammal, they have not been shown to alter fertility. Again, Applicants are claiming a universe of compounds which alter fertility while only demonstrating a few means of altering cholesterol levels in a mammal, including estrogen (Example 3 on pages 39-40 of the specification), adenoviral vector encoding SR-BI (Example 5 on pages 40-45 of the specification), and anti-SR-BI antibody (Example 8 on pages 55-66 of the specification). Appellants have not demonstrated any other compounds which alter cholesterol levels, or fertility, in a mammal.

Appellants argue that they have disclosed an extensive list of molecules on page 11 of the specification which inhibit SR-BI. However, this list includes molecules which bind SR-BI and compounds which block binding of HDL to SR-BI. It is these groups of compounds which lack the greatest written description. Appellants have only identified estrogen as belonging to one of these classes. Based on this, Appellants are claiming methods using any molecules which bind SR-BI and compounds which block binding of HDL to SR-BI. Though Appellants are claiming methods, and not the compounds themselves, Appellants still have not provided any written description of these compounds, or any effective amounts to treat reproductive disorders in a mammal, nor have Appellants shown that any of these compounds, or antibodies, or nucleic acids, are effective in this treatment. Again, Applicants have only described that knocking out the SR-BI gene produces sterile (i.e. altered fertility) transgenic female mice (Example 6, pages 45-54 of the specification). Appellant has only demonstrated that completely knocking out the SR-BI gene (i.e. from all tissues) causes female mice to be infertile (Example 6). However, in the other examples in the specification, Appellant does not describe how altering SR-BI levels in these tissues alone affects fertility or reproductive disorders in a mammal, or if altering SR-BI levels *at all* in these tissues is sufficient to alter fertility or treat *any and all* reproductive disorders in a mammal. Therefore, though Appellants have taught a method of screening for compounds which alter

fertility, as well as a method of drug design, these are general concepts, as no compounds have been described which can be used in the claimed invention. The teachings of Miettinen et al. have been considered and, though a link between cholesterol and fertility may have been established, the present specification still does not adequately describe compounds which perform the claimed function. Finally, though Appellants argue that the claims do not read on treating "any and all" reproductive disorders, the limitation in the claims of "treating a reproductive disorder" does appear to encompass any and all reproductive diseases. It is, respectfully, not understood how this limitation could be otherwise interpreted.

Claim Rejections - 35 USC § 112, first paragraph – scope of enablement

Claims 1-9, 15, 16 and 20-22 are rejected under 35 U.S.C. 112, first paragraph, lack of enablement, because the specification, while being enabling for altering cholesterol levels in female mice by knocking out the SR-BI gene, does not reasonably provide enablement for any method of altering fertility or treating *any and all* reproductive disorders by altering lipoprotein, LDL, HDL, or cholesterol levels in a mammal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Appellants argue on pages 3-5 of the Response dated 7/17/01, that the key to the present invention is the evolutionary conservation between mouse and human SR-BI and that this conservation allows for familiar and routine experimentation, via the various assays cited on page 3 of Appellant's response, dated 7/17/01 as routine in the art, to be conducted by one of skill in the art. The Appellant also argues that this evolutionary conservation also allows for careful extrapolation of the results obtained from such experimentation. Appellant further argues that ligands that bind SR-BI have been described and characterized (e.g. AcLDL, LDL, estrogen, HDL and SR-BI antibodies), that the full-length DNA encoding SR-BI is disclosed in the present specification and that the targeted sequence encoding SR-BI defines the complementary nature of the compounds to be designed. Similar arguments are made on pages 4-5 of the Response of Amendment D, filed 2/12/02 where Appellant argues that the data in the application (Examples 3, 5, 6 and 8) demonstrate that multiple compounds can be used to achieve the method of claim 1. They further support their argument by citing Miettinen et al. (J. Clin. Invenst. 108:1717-1722, 2001), who teach that SR-BI knockout mice are infertile and that fertility was restored by inactivating the apoI gene or administering the cholesterol lowering drug, probucol. **However, while these results are interesting, the infertility in these mice was induced by genetic manipulation of an**

embryonic stem cell. There is no evidence of any female reproductive disorder, including in humans, which acts via SR-BI. Appellant has produced a specific genetic alteration in a stem cell to produce this infertility in female mice and have provided no nexus between a method of altering fertility in an SR-BI knockout female mouse and a method of altering fertility or treating a reproductive disorder by altering lipoprotein, LDL, HDL or cholesterol levels in a mammal which is not an SR-BI knockout. Furthermore, the last line of the abstract of Miettinen et al. is speculative in stating that abnormal lipoprotein metabolism may contribute to some form of human infertility. **There is no evidence that altering SR-BI levels in a fertile female with normal SR-BI levels and no reproductive disorders will have the desired effect of the claimed method.** Finally, as further evidence for the lack of enablement of the present invention for any method of altering fertility or treating a reproductive disorder besides that to restore fertility in infertile SR-BI knockout female mice, that **there is no evidence in the art that women taking cholesterol-lowering drugs experience any fertility problems, demonstrating that cholesterol-lowering drugs, which would meet the limitation of claim 1, may not alter fertility.**

In considering Appellant's arguments regarding the examples in the specification demonstrating that various compounds bind SR-BI, the Examiner agrees that the specification does disclose various compounds which bind SR-BI, such as estrogen (Example 3 on pages 39-40 of the specification), adenoviral vector encoding SR-BI (Example 5 on pages 40-45 of the specification), and anti-SR-BI antibody (Example 8 on pages 55-66 of the specification). SR-BI knockout transgenic mice have also been shown to produce sterile female mice (Example 6, pages 45-54 of the specification). However, as stated by the Examiner in the previous paragraph, knocking out the SR-BI gene in an embryonic stem cell does not enable the artisan to alter fertility or to treat a reproductive disorder in a fully formed mammal by administering a compound which alters lipoprotein, LDL, HDL, or cholesterol levels, regardless of whether or not these compounds are acting through SR-BI. Therefore, Appellant still has provided no guidance or working examples of compounds which alter fertility, or treat reproductive disorders by altering lipoprotein, LDL, HDL, or cholesterol levels in a mammal other than in knockout infertile female mice, regardless of whether or not these compounds act via SR-BI. These issues are addressed in the following paragraphs of this rejection.

In In re Wands, 8USPQ2d, 1400 (CAFC 1988) page 1404, the factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

First, the breadth of the claims is excessive. Claim 1, from which all claims in the present application ultimately depend, recites a method for altering fertility, or treating a reproductive disorder in a mammal, comprising administering a compound altering lipoprotein, LDL, HDL, or cholesterol levels in the mammal. However, Appellant has provided no guidance and working examples of any compounds which act via SR-BI to alter fertility other than those in knockout infertile female mice. In fact, in the specification, estrogen (Example 3 on pages 39-40 of the specification), adenoviral vector encoding SR-BI (Example 5 on pages 40-45 of the specification), and anti-SR-BI antibody (Example 8 on pages 55-66 of the specification) have only been shown to affect SR-BI and to alter cholesterol and lipoprotein levels, but have not been shown to alter fertility or to treat a reproductive disorder in a mammal. The only method of altering fertility in a mammal that has been demonstrated by the present invention is that showing that SR-BI knockout transgenic female mice are infertile (Example 6, pages 45-54 of the specification). However, a method of knocking out a gene in an embryonic stem cell is not comparable to a method of altering fertility or treating a reproductive disorder in a developed mammal.

The instant fact pattern is similar to that in *In re Hyatt*, 708 F.2d 712, 218 USPQ 195 (Fed. Cir. 1983), wherein a single means claim which covered every conceivable means for achieving the stated purpose was held nonenabling for the scope of the claim because the specification at most disclosed only those means known to the inventors. When claims depend on a recited property, a fact situation comparable to *Hyatt* is possible, where the claim covers every conceivable structure (means) for achieving the stated property (result) while the specification discloses at most only those known to the inventor.

Furthermore, the claims of the present invention recite, or read on, altering SR-BI receptors in *any* tissue. Applicant has provided no guidance or working examples of which specific tissues modulation of SR-BI would be required in order to alter fertility or to treat *any and all* reproductive disorders. Again, Appellant has only demonstrated that completely knocking out the SR-BI gene (i.e. from all tissues) causes female mice to be infertile (Example 6). In Examples 3 and 4, Appellant has only shown that estrogen-treated rats show an upregulation of SR-BI in adrenal membranes (page 39, line 30 – page 40, line 1) and ovaries (page 40, lines 20-23). Appellant has also demonstrated the effect of hepatic SR-BI overexpression on plasma cholesterol levels (Example 4, especially page 41, lines 12-14 and Table 1). However, no nexus between SR-BI expression in these tissues and the ability to alter fertility or reproductive disorders has been made. It would also be unpredictable to one of ordinary skill in the art how to alter fertility or treat *any and all* reproductive disorders simply by altering lipoprotein, HDL, LDL, or cholesterol levels in a mammal, especially since fertility and reproductive disorders all have a separate

mechanism of action, and, in the absence of guidance or working examples, the artisan would not be able to predict which of either lipoprotein, HDL, LDL, or cholesterol, to alter, and to what extent and length of time, in order to produce the desired conditions (i.e. alter fertility or treat a reproductive disorder), especially given that each of these conditions has its own etiology and is likely affected differently by lipoprotein, HDL, LDL, or cholesterol than are the other conditions. This unpredictability is further supported by the fact that Appellant has provided no guidance or working examples of any method of altering fertility or treating a reproductive disorder by administering *any* compound which alters lipoprotein, LDL, HDL, or cholesterol levels.

In summary, the breadth of the claims is excessive regarding a method for altering fertility, or treating any and all reproductive disorders in a mammal comprising administering *any* compound altering lipoprotein, LDL, HDL, or cholesterol levels in the mammal in *any* specific tissue. Appellant has only shown that a complete knockout of the SR-BI gene alters fertility in female mice. There is also a lack of guidance or working examples of any method altering fertility or treating a reproductive disorder in a mammal by altering lipoprotein, HDL, LDL, or cholesterol levels, as well as any methods altering male fertility by altering these levels. These factors, in addition to the lack of predictability of which of either lipoprotein, HDL, LDL, or cholesterol, to alter, and to what extent and length of time, in order to produce the desired conditions (i.e. alter fertility or treat a reproductive disorder), lead the Examiner to hold that undue experimentation is necessary to practice the claimed invention.

(11) Response to Argument

Claim Rejections - 35 USC § 112, first paragraph – written description

In the Appeal Brief filed 5/15/06, Appellants argue that they are the first to recognize that lipoprotein and/or cholesterol levels affect a female's ability to reproduce and that by using SR-BI knockout mice, the SR-BI receptor plays a role in this ability. Appellants have also demonstrated that cholesterol-lowering drugs restore fertility. Examples 5-8 demonstrate the effect of SR-BI or SR-BI antibodies on cholesterol levels.

First, the Examiner is confused. In the second paragraph on page 5 of the Brief, Appellants state that increased SR-BI expression *decreases* cholesterol levels. However, in the paragraph bridging pages 5-6, it appears that an increase in SR-BI expression *increases* cholesterol levels. Second, Appellants argue that the claimed invention is based on the clear-cut description of the nexus between fertility and cholesterol levels. They argue that since the specification is replete with support for this novel connection the appellant is entitled to claim all compounds that alter lipoprotein, LDL, HDL, or cholesterol levels for

the purpose of altering fertility or treating a reproductive disorder in a female mammal. Appellants argue that antibodies raised against a portion of the extracellular domain of SR-BI protein inhibit selective uptake of HDL in cultured adrenal cells (Example 8 of the specification) and that adenoviral vectors encoding SR-BI alter cholesterol levels (Example 5). Therefore, the specification discloses specific compounds which alter cholesterol levels.

This argument has been considered, but is not deemed persuasive. Again, Applicants are claiming a method of altering fertility or treating a reproductive disorder in a female by altering cholesterol levels. As previously stated, knocking out the SR-BI gene in an embryonic stem cell does not demonstrate the ability to alter fertility or to treat a reproductive disorder in a fully formed mammal by administering a compound which alters lipoprotein, LDL, HDL, or cholesterol levels, regardless of whether or not these compounds are acting through SR-BI. These examples only show that Appellants were in possession of compounds which alter cholesterol levels, not which alter fertility or treat reproductive disorders in a female mammal. Therefore, though Appellants may be correct in stating that "one of ordinary skill in the art will readily recognize not only the direct correlation that exists between cholesterol/HDL and the existence of SR-BI, but also the many compounds that already exist for regulating cholesterol levels," Appellants, respectfully, have only demonstrated just that. They have not demonstrated that they are able to perform the claimed methods, but only the relationship between cholesterol and SR-BI. This can further be seen by comparing claims 4 and 5 as well as 6 and 7. Claims 4 and 6 recite decreasing SR-BI levels, whereas claims 5 and 7 recite increasing SR-BI levels. Therefore, it is not understood how Appellants have adequately supported the present invention when the claims recite either an increase or decrease in SR-BI levels. This adds further support that Appellants were not in possession of the claimed invention since it is not known in which direction SR-BI must be altered in order to treat a specific disease, or to alter fertility.

Appellants have stated on page 14 of the Brief that it is not clear why the subject matter of claims 2-7, 15, 16, 19 (withdrawn) and 20 lack proper written description. Although Appellants may have disclosed specific mechanisms of how to alter SR-BI expression, Appellants still have not enabled the claimed invention of *altering fertility or treating a reproductive disorder* in a mammal for the reasons given above. The issues relating to each group are not different for each of the foregoing groups. The fact remains that the intention of this method, to alter fertility or treat reproductive disorders in a mammal using the claimed mechanisms, is not adequately described for the reasons stated above. Therefore, regardless of the means of altering cholesterol, Appellants have not adequately described the invention of

altering fertility or treat reproductive disorders in a mammal. These reasons are no different than those stated above.

Claim Rejections - 35 USC § 112, first paragraph – scope of enablement

Appellants argue that the Wands factors must be considered when determining whether or not an invention is enabled and that there is no requirement for examples. Appellants argue that the specification is replete with support for a connection between cholesterol levels and fertility. Because of Appellants' novel discovery, they argue that they are entitled to all compounds which alter lipoprotein or cholesterol levels for the purpose of altering fertility in a mammal and that the class of patients encompassed by the claims is relatively small. While it may be true that the class of patients is relatively small and may not overlap other groups of patients, the fact remains that Appellants have not demonstrated that they are in possession of the claimed invention. Appellants have only demonstrated that they are in possession of compounds which alter cholesterol and that fertility can be restored in transgenic mice lacking the SR-BI gene by administering cholesterol-lowering drugs. This would likely be acceptable if Appellants were claiming a method of increasing fertility in transgenic mice lacking the SR-BI gene, or methods of altering cholesterol levels by modulating the SR-BI receptor, but this is not the case. Appellants have taken their one example using a transgenic mouse and, respectfully, basically combined it with their in vitro data using antibodies and estrogen to conclude that these cholesterol-lowering drugs can alter fertility in a female mammal, or can treat every conceivable reproductive disorder, when the specification enables none. This can further be seen in the claims. Claims 4 and 6 recite decreasing SR-BI levels, whereas claims 5 and 7 recite increasing SR-BI levels. Therefore, it is not understood how Appellants have adequately supported the present invention when the claims recite either an increase or decrease in SR-BI levels. This adds further support for a lack of enablement since Appellants are not able to specify in which direction SR-BI must be altered in order to treat a specific disease, or to alter fertility.

Appellants have stated in the Brief that it is not clear why the subject matter of claims 2-7, 15, 16, 19 (withdrawn) and 20 are not enabled since they recite specific means of altering SR-BI. However, though Appellants may have taught the artisan how to altering SR-BI expression, Appellants still have not enabled the claimed invention of *altering fertility or treating a reproductive disorder* in a mammal for the reasons given above. Though the ability to decrease SR-BI expression is, as stated by Appellants, different from generally decreasing cholesterol level, the fact remains that the intention of this method, to alter fertility or treat reproductive disorders in a mammal, is not enabled, again, for the reasons stated above. Therefore, regardless of the means of altering cholesterol, Appellants have not enabled the

invention of altering fertility or treat reproductive disorders in a mammal. These reasons are no different than those stated above.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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May 25, 2006

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